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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/670,626	09/25/2003	Xiaodong Wang	UTSD:1493	6739

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EXAMINER	
WOLLENBERGER, LOUIS V	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/670,626	WANG ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) *5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 5/172006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 9/1/2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 5/17/2006, claims 1-4 are pending in the application and currently under examination.

Response to Arguments—Claim Rejections - 35 USC § 112

Claims 1–4 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Though the amendment of 5/17/06 narrows the scope of the claims, the claims remain broad. For example, in their broadest embodiments the claims include methods for making siRNA by recombinantly coexpressing any dicer protein from any organism with any *Drosophila* R2D2 protein, including any variants or isoforms thereof. Similarly, although claims 2 and 4 are

narrower in scope than claim 1, claims 2 and 4 encompass any *Drosophila* R2D2 protein and any *Drosophila* dicer-2 protein.

As noted in the previous Office Action, the recombinantly expressed proteins are recited by name only, without providing any specific identification of the particular amino acid sequence or cDNA sequence to be expressed. That is, the instant claims are generic in that they do not refer to any particular protein or cDNA sequence, as by SEQ ID NO: or other identifying features or structures such that one of skill in the art would immediately recognize which proteins and sequences are to be used in the instant methods.

While the instant specification adequately describes one particular R2D2 protein by identifying the protein as that encoded by GenBank Accession No. NM_135308, the specification does not adequately describe any particular or exemplary dicer or dicer-2 protein or gene sequence for coexpression with R2D2.

That is, the particular features that set Dicer-2 apart from other proteins, including other Dicer proteins, are unclear. Applicants describe DCR-2 by name and function only and provide no readily identifiable structure or sequence showing one of skill in the art which sequence in particular is to be coexpressed with R2D2 (NM_135308). The Dicer proteins and dicer-2 proteins required for the instant methods are recited in terms of their function only, there is no art-recognized correlation between the structure and function, and the specification does not provide the support needed to enable one skilled in the art to predict with a reasonable degree of confidence the structure of the claimed Dicer proteins from a recitation of their function only.

To be clear, it cannot be readily ascertained from the instant application which Dicer protein(s) is/are to be coexpressed in the instant methods. No SEQ ID NO: identifiers or

GenBank Accession numbers have been provided such that one of skill would be able to recognize the protein(s) that applicants are claiming for coexpression with R2D2. A review of the GenBank database indicates that DCR-2 corresponds to hundreds if not thousands of possible sequences. As a result, it is unclear what Dicer proteins are being claimed in the instant invention. Which particular Dicer cDNA sequences are to be coexpressed with R2D2 (NM_135308)? It is unclear, and a review of the instant application fails to find any identifying features or characteristics, or any description of a structure/function correlation that would enable one of skill to immediately envision which dicer proteins are to be coexpressed in the instant methods.

Thus, applicants have not shown possession of the claimed methods using any and all possible Dicer proteins and dicer-2 proteins. Rather Applicants invention is directed to a specific complex composed of two distinct *Drosophila* proteins designated R2D2, corresponding to NM_135308, and DCR-2, whose particular structural features, sequence, and characteristics are unclear.

With the exception of those specific, structurally and functionally defined proteins and gene sequences disclosed in the specification (e.g., R2D2, NM_135308), the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of dicer proteins and dicer-2 proteins that satisfy each of the criteria delineated in the claims, regardless of the complexity or simplicity of the methods used to screen and identify such proteins.

Thus, adequate written description does not exist for the entire scope of the invention as now claimed, because the specification describes neither a representative number of species nor a

structure/function correlation such that one of skill in the art would recognize Applicants were in possession of the genus of methods now claimed at the time the application was filed.

Applicants' arguments addressed:

Applicants cite several references and point to page 1 of the specification to show that Dicer proteins comprise a large, well known family of RNase III enzymes (Remarks, page 4). Applicants argue that those skilled in the art recognize the scope and meaning of the recited Dicer and R2D2 proteins. In support thereof, Applicant Liu has submitted a Declaration under 37 CFR §1.132, stating that one of skill in the art would have no trouble substituting one known dicer protein for another in the assay. The declaration further states that the claims require an enzymatic activity, and that the skilled practitioner would need only to perform routine screening to confirm the candidate protein is operative in the method.

Applicants' remarks have been fully considered but are not found persuasive.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

"To fulfill the written description requirement, the patent specification 'must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.'" (Gentry Gallery, Inc. v. Berkline Corp., 134 F.3d 1473, 1479, 45 USPQ2d 1498,

1502-03 [Fed. Cir. 1998]). "A disclosure in a parent application that merely renders the later-claimed invention obvious is not sufficient to meet the written description requirement; the disclosure must describe the claimed invention with all its limitations." (Tronzo v. Biomet Inc., 156 F.3d 1154, 1158, 47 USPQ2d 1829, 1832 [Fed. Cir. 1998]).

The written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

As applicants state in their remarks and in the Declaration, the genus of dicer proteins encompassed by the instant claims is large, and structurally diverse. As an example, the instant application itself shows that Drosophila cells encode at least two different dicers and that the siRNA-generating activity is predominantly associated with one dicer, dicer-2. Thus, it would appear that even in a single organism one would be left to de novo screening to identify any and all possible siRNA-generating isoforms.

The fact that one of skill in the art can isolate or screen for a particular substance using conventional techniques is not dispositive to the analysis of written description. The question of written description is not based on the simplicity or ease with which dicer and other R2D2 proteins may be isolated, but on a description of the particular structural features and characteristics of the dicer and R2D2 proteins themselves. Rather than describing the dicer and all R2D2 proteins themselves, Applicant is simply inviting one of skill to experiment and engage in empirical testing to identify all other potential products for use in the claimed invention.

Accordingly, the instant claims stand rejected for lack of written description support.

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Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1–4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

methods of making siRNA *in vitro* by coexpressing a *Drosophila* Dicer-2 protein and *Drosophila* R2D2 protein, encoded by GenBank Accession No. NM_135308 to form a complex and then contacting the complex with dsRNA *in vitro* in a *Drosophila* cell lysate to form siRNA *in vitro* in a *Drosophila* cell lysate,

does not reasonably provide enablement for:

methods of making siRNA *in vivo* in any organism, including humans and other mammals, by coexpressing any dicer protein, including any *Drosophila* Dicer-2 protein with any *Drosophila* R2D2 protein to form a complex and then contacting the complex with dsRNA *in vivo* in cells *in vivo* in any animal or organism to form siRNA *in vivo* in any organism.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

The claims as written encompass methods of making siRNA in cells *in vitro, in vivo*, or *ex vivo*. Claims 3 and 4 limit the invention by requiring the coexpression step to take place in a baculovirus expression system. Claims 1 and 2 are considered to include methods of RNAi, wherein recombinant coexpression takes place *in vivo*.

The invention is considered to be in a class of invention that the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Thus, the invention includes embodiments that specifically require the delivery of recombinant expression constructs or products thereof to target cells or tissue.

MPEP §2164.08 states in part that :

"The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." *In re Wright,* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Nevertheless, not

> everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)."
>
> "As concerns the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. >*AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244, 68 USPQ2d 1280, 1287 (Fed. Cir. 2003);< *In re Moore*, 439 F.2d 1232, 1236, 169 USPQ 236, 239 (CCPA 1971). See also *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1339, 65 USPQ2d 1452, 1455 (Fed. Cir. 2003) (alleged "pioneer status" of invention irrelevant to enablement determination)."
>
> "The determination of the propriety of a rejection based upon the scope of a claim relative to the scope of the enablement involves two stages of inquiry. The first is to determine how broad the claim is with respect to the disclosure. The entire claim must be considered. The second inquiry is to determine if one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation."

In the instant case, the claimed methods encompass the modulation of gene expression in cells *in vivo* in animals by sequentially delivering recombinant expression plasmids or recombinant products, such that the recited proteins are first coexpressed and then contacted with dsRNA in any cell in any animal. A review of the instant application fails to find sufficient disclosure enabling the full breadth of the instant claims in that neither the prior art nor the specification teaches one of skill in the art at the time the application was effectively filed how to sequentially or concurrently coexpress dicer and R2D2 proteins in cells *in vivo* in any animal to produce siRNA *in vivo*.

Pre- and Post-filing art indicates that the art of *in vivo* delivery of nucleic acids into targeted cells, tissues, and organs was highly unpredictable at the time the instant application was effectively filed. Unpredictability in the art stems mainly from the inability to routinely deliver

an effective concentration of a specific nucleic acid into a target cell, such that a target gene is inhibited to a degree necessary to produce a diagnostic or therapeutic effect.

For instance, Gerwirtz et al. (1998) *Blood* 92(3):712-736 teach that

> "...delivery of oligonucleotides remains an important problem..." (page 728). "The ability to deliver ODN into cells and have them reach their target in a bioavailable form must be further investigated. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient." (page 728)

Similarly, Greco et al. (2002) *Frontiers in Bioscience* 7:d1516-1524 teach that, while gene therapy represents a promising approach for the treatment of cancer and other genetically-based diseases, major problems remain to be solved before this strategy becomes routinely adopted. Chief among them is the problem of gene delivery. Vectors must be protected from immune attack and capable of delivering the transgene to the target cell(s) in an efficient manner to ensure uptake and expression at the required level (page 1516). Greco et al. state, for example, that while progress has been made in recent years, delivery of DNA to tumor sites remains a formidable task (page 1517)

A review of the instant application fails to find any working examples or representative teachings enabling or demonstrating the delivery of one or more recombinant expression constructs or recombinantly coexpressed proteins or protein complexes, or dsRNA to cells *in vivo* to produce siRNA in vivo.

Given the unpredictability in the art of nucleic acid delivery and uptake *in vivo*, the skilled artisan would require specific guidance from the instant application to practice the claimed methods to make siRNA in any cell in any animal *in vivo*.

Specific guidance would be required to teach one of skill in the art how to effectively deliver nucleic acids such as recombinant expression vectors and the required dsRNA to any cell in any tissue, including brain and central nervous system tissue, in any animal to provide for the production of siRNA.

The primary factors appear to be delivery, uptake, stability, and biological effect in host organisms, which cannot be predicted *a priori* based on cell culture experiments and direct injection animal models.

Moreover, the lack of enablement is heightened in this case by the fact that not one, but two different proteins must be recombinantly coexpressed so as to form a complex with one another. Presumably, based on the *in vitro* examples presented at pages 4-8, the proteins must interact or be present together in the same cell or, at least, the same cell population to have the disclosed effect of suppressing gene expression.

The examples do not show or demonstrate methods for coexpressing and forming such complexes in cells *in vivo.*

Thus, while these examples adequately demonstrate and enable methods of making siRNA *in vitro* in *Drosophila* cell lysate, using recombinantly coexpressed *Drosophila* dicer-2 protein and *Drosophila* R2D2 protein (page 6), the specifiation does not teach methods for making siRNA *in vivo* in animals, including humans.

Cell culture examples are generally not predictive of *in vivo* methods since delivery to and expression in a cultured cell would not be applicable to delivery to and expression in any tissue and/or cell in any organism. Due to differences in the physiological conditions of a cell *in*

vitro versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

Thus, considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to use the claimed invention commensurate with the claims scope.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement in that the scope of enablement provided to one skilled in the art by the disclosure is not commensurate with the scope of protection sought by the claims.

***

Claims 1 and 3 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention.

Applicants' arguments addressed:

Applicants argue that one of skill in the art would have no trouble substituting one known dicer protein for another in the claimed method (see Remarks and Declaration under 37 CFR §1.132)..

A review of the instant application finds working examples and disclosure directed to the use of two *Drosophila* proteins, designated Dicer-2 and R2D2, which are said to cooperate as a

complex to cleave long dsRNA into short interfering RNA, or siRNA. Further, the complex is said to facilitate siRNA uptake by RISC, which is essential for RNAi in *Drosophila* cells.

While *Drosphila* R2D2 protein is readily identified as the protein encoded by NM_135308, other R2D2 sequences have not been set forth, nor has adequate guidance been given teaching one of skill how to identify, isolate, clone, and express all other conceivable R2D2 proteins in the claimed genus. Furthermore, while Applicants teach that R2D2 cooperates with Dicer-2 from *Drosophila,* and while it appears as though Dicer-2 has been previously characterized in the prior art (Bernstein et al., 2001, *Nature* 409:363-6, for example), it is, nevertheless, unclear whether any other Dicer protein or dicer-2 sequence in particular may be used for recombinant coexpression with R2D2 in the instant claims, since the prior art and sequence databases are replete with teachings of various Dicer and dicer-2 proteins and sequences from *Drosophila* and other organisms. For example, Meister et al. (2004) *Nature* 431:343-349 (cited in previous Action) teach that *Drosophila* has two paralogues, Dicer-1 and Dicer-2, which function in miRNA and dsRNA processing pathways (page 343). Four Dicer-like proteins have been identified in *Arabidopsis thaliana* (Meister et al., page 344). Which sequences of the many now disclosed for different organisms is/are suitable for coexpression with which R2D2 proteins to practice the claimed invention? While applicants describe one Dicer/R2D2 complex for making siRNA, applicants do not describe every Dicer/R2D2 complex such that the skilled artisan could recombinantly coexpress and make every complex, as now required.

Furthermore, it is unclear how one of skill is to recognize and identify all other putative dicer proteins for use in the instant claims. The specification teaches only that dicer has an art-

recognized function as having the capability of generating siRNA (page 5-6). However, the specification also teaches that many different RNase III proteins are known (page 1), and that some are capable of forming complexes with R2D2 and generating siRNA, while others are, apparently, less prone to forming complexes with R2D2 and generating siRNA (page 5, lines 25-26). Moreover, the instant application teaches that R2D2 in fact does not affect the ability of DCR-2 to recruit or cleave dsRNA *in vitro*, but that it may stabilize DCR-2 and thereby positively regulate siRNA production in *Drosophila* cells (page 7). How, then, is one of skill to identify all putative dicer and *Drosophila* R2D2 proteins and complexes thereof having the ability to positively regulate siRNA production in *Drosophila* cells? No particular assay or detection method has been taught or suggested.

Considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to practice the claimed invention commensurate with the claims scope.

Accordingly, the instant claims stand rejected for failing to comply with the enablement requirement.

Response to Applicants' Arguments

Applicants' arguments presented on 5/17/06 not specifically addressed above are considered to be moot in view of Applicants' amendments to the claims and in view of the new and/or reiterated rejections stated herein, above.

Applicant's Declaration under 37 CFR §1.132 has been fully considered, but has not been found persuasive for the reasons given above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571)272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Louis Wollenberger
Examiner, Art Unit 1635
June 13, 2006

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER